REMARKS

Support of Claim to Priority

The Examiner has denied the claim to priority to Swedish application Nos. 9402487-4 and 9403953-4, with the assertion that the priority documents do not support sequencing of the complete coding region of p53.

The present invention is drawn to a method in which a nucleotide sequence of the complete coding region of a cancer-related p53 protein from genomic DNA or cDNA derived from a human neoplastic tissue or body fluid is determined. Thus, the present invention is clearly drawn to determination of the sequence of the coding region of the human p53 gene. In humans, as with many other species, exon 1 is not expressed. As such, sequencing of exons 2-11, as disclosed in the present specification and priority documents, is sequencing of the complete coding region. This is shown in Figures 2 and 3 of the specification, wherein exons 2-11 are designated as the coding region. As such, the present invention as claimed is fully supported. Acknowledgement of the claim to priority is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-11, 13, 14 and 15 have been rejected under 35 U.S.C. § 112, first paragraph for containing matter not supported originally filed specification. Specifically, the Examiner asserts that the specification does not support recitation of determining the sequence of the complete coding region of the p53 gene, but only sequencing exons 2-11. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As discussed above regarding the claim to priority, humans do not express exon 1. Thus, sequencing exon 2-11, as disclosed in the specification is, in fact, sequencing of the complete coding region. The presently claimed invention is therefore fully supported by the specification as originally filed and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-10 and 14 have been rejected under 35 U.S.C. § 103 as being obvious over Elledge et al., Callahan and the newly cited reference of Diamandis et al. Elledge et al. and Callahan are generally relied on as before. Diamandis et al. is asserted to teach that "sequencing the entire coding region as the most specific method" for diagnostic/prognostic methods with p53.

Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As discussed in the Preliminary Amendment of July 19, 1999 Elledge et al. do not disclose or suggest sequencing of the complete p53 coding region and not all samples were sequenced in any way. The only sequencing done in Ellege et al. was a limited partial sequence analysis of those mutations, which were identified using SSCP. Similarly, there is no suggestion in Callahan of sequencing the complete p53 coding region and optionally combining such sequence information with nodal status, nor is there any suggestion in Callahan of the advantages associated with such a method.

The Examiner newly relies on Diamandis et al. for overcoming the deficiencies of Ellege et al. and Callahan et al. and teaching the sequencing of the complete p53 coding region. Applicants traverse this rejection in that Diamandis et al. fails to overcome the deficiencies of Ellege et al. and Callahan et al. and does not, in fact, teach sequencing the complete p53 coding region.

Diamandis et al. discloses a three level hierarchy for p53 diagnosis. See Figure 1. On the first level method of Diamandis et al. starts with immunohistochemical analysis for detecting the presence of p53 protein products. However, as Diamandis et al.

teach in column 4, final paragraph, spanning column 5, level 1 immunohistochemical analysis is limited in that it will not detect cancer patients who have mutations resulting in p53 not being expressed, i.e. nonsense mutations. Thus, unless other analysis is performed relevant patients may be excluded from detection using level 1. The disclosed advantage of level 1 analysis is that the costs are minimized compared to level 2 and 3 analysis. See column 3, line 63 through column 4, line 3. However, this financial cost savings is at the expense of missing patient who have potentially severe p53 mutations.

The Examiner relies on the level 3 analysis method as teaching "sequencing the entire coding region was the most accurate and specific method." However, nowhere does Diamandis et al. teach sequencing the complete coding region is desired. The portions of Diamandis et al. referenced by the Examiner, i.e. Figure 1, column 2, lines 13-27 and column 5, lines 20-23, are indefinite with regard to "what" should be sequenced from p53. Thus, it is not clear from the referenced portions of the specification, how much of the p53 gene should be sequenced in the method of Diamandis et al.

However, what is not clear in the specification is very clear from the claims of Diamandis et al. and it is very clear from the

claims that sequencing the complete coding region was not contemplated as advantageous. Diamandis et al. recites 60 claims, 54 of which are directed to sequencing steps. Of these 54 claims, not a single one suggests sequencing the complete coding region of p53. In fact, the claims of Diamandis et al. teach away from the need to sequence the complete coding region by reciting "sequencing at least one exon"; "sequencing at least some of the exons" and most notably 22 claims specifically recite the sequencing of a single exon. Thus, not only does Diamandis et al. fail to teach sequencing the complete coding region of p53, the reference actually teaches away from a need to sequence the complete coding region. As such, Diamandis et al. fails to overcome the deficiencies of Ellege et al. and Callahan et al. The present invention is therefore not obvious over the combined references and withdrawal thereof is respectfully requested.

Claims 11, 13 and 15, have been rejected as being anticipated by Hollstein et al.; Hedrum et al. and Diamandis et al. Claims 11 and 13 have been cancelled thus obviating these rejections. Applicants traverse the rejection regarding claim 15 as being anticipated by Diamandis et al. and withdrawal thereof is respectfully requested.

Claim 15 is drawn to a method of prognostication of the development of neoplasia in a patient having neoplasia comprising determining the sequence of the complete coding region of p53. As noted above, Diamandis et al. fails to disclose sequencing the complete p53 coding region. As such, the present invention, as encompassed by claim 15 is not anticipated by Diamand is et al. Withdrawal of the rejection is, therefore respectfully requested.

As the above-presented amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and reconsideration and allowance of the claims are respectfully requested. Should the Examiner have any questions regarding the present application, she is requested to contact MaryAnne Liotta, PhD (Reg. No. 40,069) in the Washington DC area, at (703) 205-8000.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of two (2) months to March 13, 2000 in which to file a reply to the Office Action. The required fee of $380.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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